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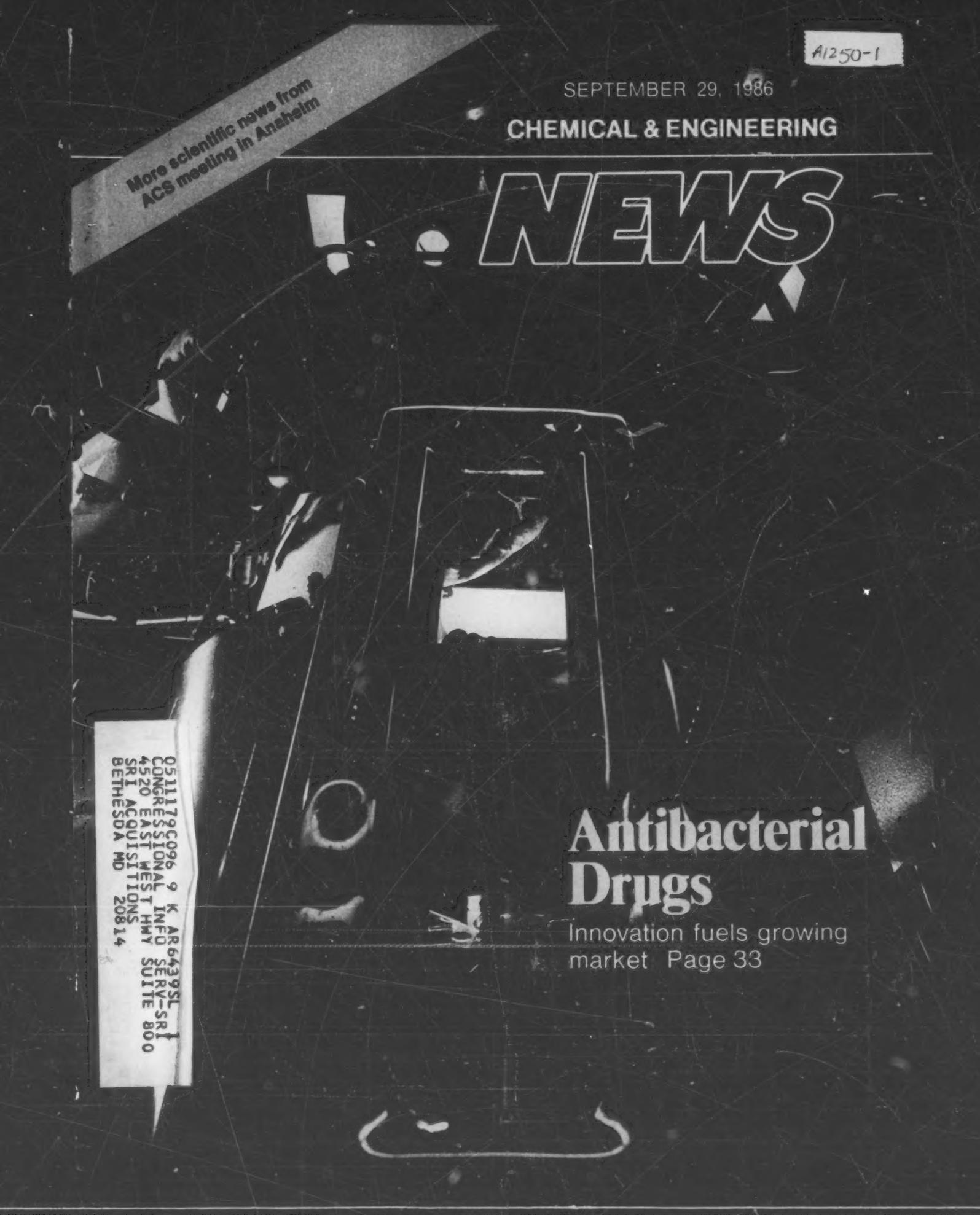
CHEMICAL & ENGINEERING

NEWS

More scientific news from ACS meeting in Anaheim



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Antibacterial Drugs

Innovation fuels growing market Page 33

CHEMICAL & ENGINEERING
NEWS

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News of the Week

■ **Limited success of azidothymidine in clinical trials is leading scientists and health officials to reassess testing procedures in treatment of AIDS.** **Page 6**

■ **Air Products & Chemicals names its president, Dexter F. Baker, to succeed Edward Donley as chairman and chief executive officer.** **Page 7**

■ **National Distillers & Chemical's planned purchase of Enron Chemical and divestiture of spirits and wine segment will make it nation's largest producer of polyethylene and shift its focus to chemicals.** **Page 7**

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ACS News

Councilors adopt Target 2000 planning document, approve two bylaw amendments. **Page 81**

Congressional fellows for 1985–86 express satisfaction at end of year's work on Capitol Hill. **Page 84**

Cover: Pilot-plant-scale fermentation unit at Squibb Institute for Medical Research, Princeton, N.J., used to help identify and characterize bacteria and to find optimum conditions for producing new antibiotics

Product Report

Antibacterial drug market, fueled by innovation, is experiencing feverish growth worldwide; in next five years more than three dozen new antibacterials will be processed by FDA. **Page 33**

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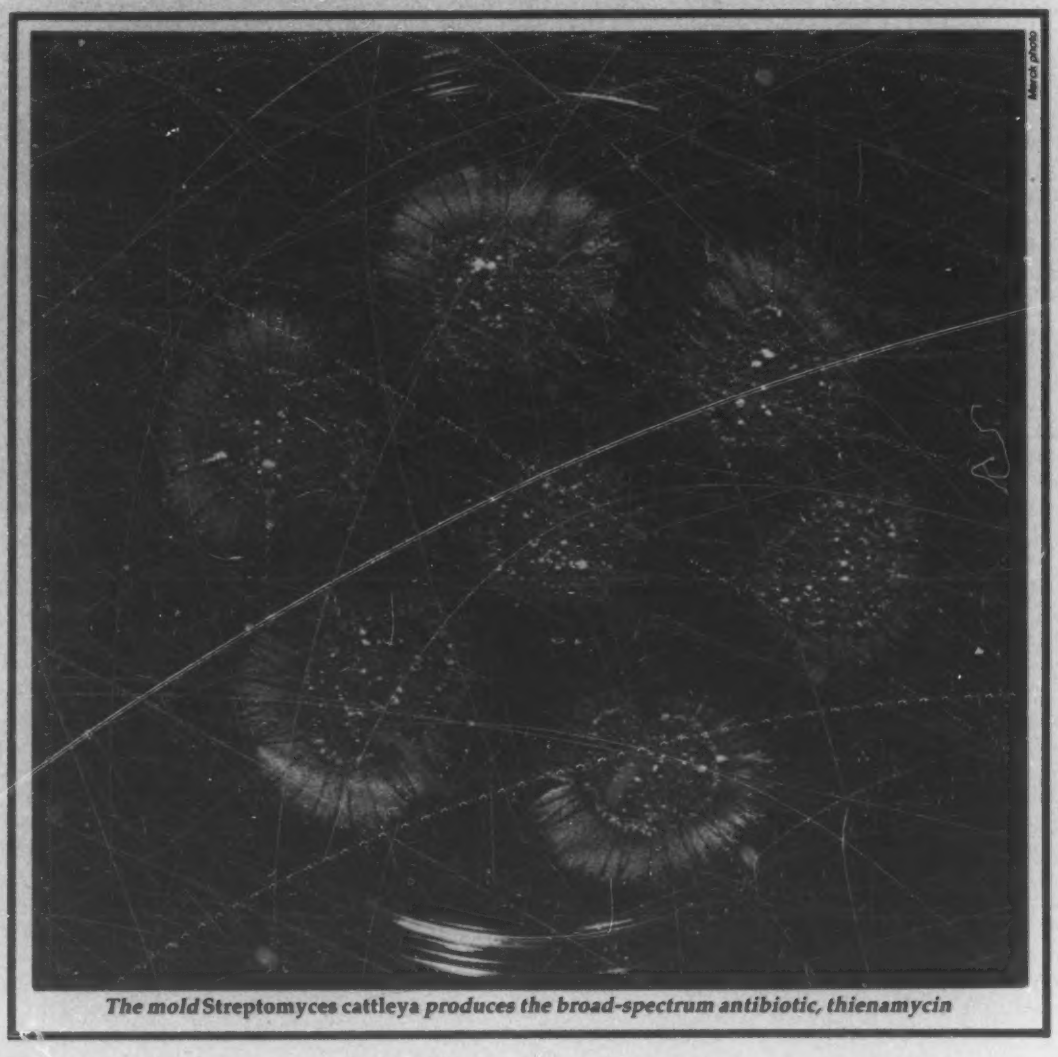

The mold **Streptomyces cattleya** *produces the broad-spectrum antibiotic, thienamycin*

Innovation Fuels Growing Market For Antibacterial Drugs

Stephen C. Stinson, C&EN New York

Research on and development of antibacterial drugs have reached feverish levels of activity worldwide. In the U.S. alone, more than three dozen new antibacterials will wend their slow routes through the Food & Drug Administration in the next five years. True, cost-cutting pressures from governments combined with price competition from generic forms will erode sales and profits in this period.

But higher prices for new, more potent, patent-protected antibacterials will more than offset these losses. David K. Crossen, security analyst at the investment management firm of Sanford C. Bernstein & Co., New York City, estimates that U.S. sales will grow 5% yearly from $2.5 billion in 1985 to $3 billion in 1990.

Some of the fuel for the current push in antibacterials comes from the seemingly inexhaustible supply of molecular structures in nature. Prospecting among new molds, chemists at Merck & Co. found thienamycin, a penicillin that lacks the usual heterocyclic sulfur atom. The resulting carbapenem class of antibiotics is the object of dogged research everywhere, with Merck's own injectable product having the

broadest spectrum of any antibiotic known to date.

And at Squibb Corp., sifting through countless soil samples has yielded molds that make antibiotics with bare azetidinone rings. So even the fused five- and six-membered rings of β-lactam antibiotics, let alone their heterocyclic sulfur, are unneeded for activity. Other firms have rushed to develop compounds in this monobactam class, though Squibb will come to market first with its injectable aztreonam.

More fuel to develop new antibacterials comes from purely synthetic chemistry. Medicinal chemists have regained confidence that quinolones can be developed with broader spectra and lower incidence of side effects than earlier compounds of the class.

Richard R. Vietor, security analyst at Merrill Lynch in New York City, surveyed prospects for the newest generation of quinolones, which are oral drugs. Vietor predicts that Merck will be first into the U.S. market with norfloxacin, followed by the enoxacin of Warner-Lambert, and then by the ciprofloxacin of Miles Laboratories.

Although the bounty of nature and the inventiveness of medicinal chemists provide the push that brings new antibacterials to market, other forces are pulling them along, too. One force is cost-containment measures. The U.S. government has set up diagnostic-related groups (DRGs) in the medicare system, under which amounts reimbursed will be fixed according to the disease diagnosed rather than the actual amount spent to treat it. Crossen of Bernstein & Co. has analyzed the effects of DRGs on antibacterials.

Squibb workers collect soil samples in Pine Barrens region of New Jersey

Crossen expects hospital managers to shorten the length of patient stays over the next five years. Thus, doctors will use fewer injectable and more oral antibacterials to treat infections because injectables must be given by medical personnel, whereas patients can take oral prescriptions at home. In addition, doctors must order costly laboratory tests to monitor injectable aminoglycoside antibiotics to avoid possible damage to kidneys and hearing. This growing preference for oral drugs will pull the quinolones along, as well as oral forms of such newer antibiotics as monobactams.

A second force exerting a pull on new antibacterials is continuing concern over development of resistant bacteria. As hospitals turn to wide use of broad-spectrum antibacterials, populations of bacteria resistant to each of these evolve. Hospital personnel cannot help but be carriers of resistant bacteria. About 6% of patients acquire a bacterial infection while in the hospital.

But cost-containment measures also can work against antibacterial drug sales. For example, Crossen already sees that hospitals are led to use fewer antibacterials before surgery as prophylaxis against infection.

Another effect of cost containment is that hospitals are limiting the number of antibiotics included in hospital formularies as available for use. Crossen sees sales and profits eroding as drug firms bid to get their antibacterials listed. Such competition will intensify as a large number of new antibacterials come to market by 1990, he says. Another factor is the great number of broad antibacterial drug categories, which may be represented on formularies by only a few compounds each.

Examples of newer antibacterials that satisfy these concerns are Hoffmann-La Roche's injectable cepha-

Antibacterials: what they are

This Product Report covers drugs with antibacterial activity, which include the antibiotics. Medicinal chemists call an antibiotic any antibacterial compound that comes from such natural sources as molds, or a compound that has a molecular structure analogous to natural antibacterials. Thus, penicillin G is an antibiotic produced from fermentation of *Penicillium chrysogenum*. Aztreonam is also an antibiotic, even though made synthetically, because soil molds produce compounds that have its basic azetidinone nucleus. Antibacterials that are not antibiotics include quinolones, nitrofurans, and sulfa drugs.

This report does not include antifungal, antiviral, or antiparasitic drugs, though some antibacterials are active against some of those infection types also. For example, penicillin G is the drug of first choice for syphilis, which is caused by a spirochete. And tetracyclines are preferred against the rickettsia of Rocky Mountain spotted fever.

Some compounds originally discovered by their antibiotic activity are later found to be anticancer drugs also. Mitomycins, produced by fermentation of *Streptomyces caespitosus*, apparently inhibit replication of bacterial DNA by crosslinking the strands, and may damage DNA of human malignant cells in the same way.

losporin, ceftriaxone; Merck's injectable carbapenem formulation, Primaxin; and Pfizer's injectable cephalosporin, cefoperazone.

Ceftriaxone has the longest serum half-life of any cephalosporin, which means that doctors can give it only once daily to patients whose infections respond to it. This is important, because nursing and pharmacy costs combine with drug costs to make up the total cost of antibacterial therapy, so fewer doses are less expensive overall.

Primaxin contains a thienomycin derivative called imipenem, which has the broadest spectrum of any antibacterial. That means that doctors can give Primaxin as a single drug in emergencies when laboratory tests have not yet identified

Chemicals celebrate a century of combat against bacteria

Ever since doctors found that bacteria cause disease, chemists have sought and perfected the "magic bullets" to kill them.

1865. Joseph Lister, surgeon at the Glasgow Royal Infirmary, uses aqueous phenol to disinfect instruments, wounds, incisions, and air. By 1869 mortality on his ward drops to 15% from 45%.

1876. Prussian country doctor Robert Koch isolates bacteria from animals with anthrax, cultures them, and shows that they induce the disease in other animals. His classic method of proof finds wide use in linking microorganisms to disease, and he receives the Nobel Prize in 1905.

1877. Louis Pasteur, physiological chemist at the École Normale Supérieure, Paris, finds that invading atmospheric bacteria kill anthrax germs in cultures, that anthrax germs cannot survive in soil, and that animals infected by other germs are not infected by anthrax. This antagonism among microorganisms is later called antibiosis.

1898. Bacteriologist Rudolph Emmerich of the University of Munich [illegible] bacteriocidal pyocyanase from *Pseudomonas aeruginosa*. Though moderately successful in patients, pyocyanase is abandoned as unreliable and toxic by 1913.

1910. Paul Ehrlich, director of the Royal Institute for Experimental Therapy, Frankfurt, tries 605 arsenic compounds against microbes and finds that No. 606, arsphenamine, is effective against *Treponema pallidum*, the syphilis spirochete. Ehrlich, who had won the Nobel Prize in 1908 for work on immunology, was inspired by preferential staining of certain tissues with methylene blue. He theorized that some chemicals, which he called "magic bullets," might bind to and kill bacteria without harming human cells.

1928. Pathologist Alexander Fleming at St. Mary's Hospital, London, finds that *Penicillium notatum* molds contaminating his Staphylococcus cultures kill them. He names the inhibiting substance penicillin and realizes its importance, but lack of funds prevents him from isolating it for tests.

1932. Pathologist Gerhard Domagk of Farbenfabriken Bayer's laboratory in Wuppertal-Elberfeld, Germany, tries thousands of dyes against bacteria and discovers that 4-(2,4-diaminophenyl)-azobenzenesulfonamide cures streptococcal infections in mice. Others will find that animals metabolize the dye to sulfanilamide. Domagk wins the 1939 Nobel Prize for the sulfa drugs, but the German government forbids him to accept. Domagk gets his medal in 1947.

1938. Pathologist Howard W. Florey and biochemist Ernst B. Chain of Oxford University evaluate Fleming's penicillin, made confident of success by the known effectiveness of the sulfa drugs. They come to the U.S. in 1941 at the outbreak of war to arrange commercial production. Fleming, Florey, and Chain share a Nobel Prize in 1945.

1939. Bacteriologist René Dubos of Rockefeller Institute for Medical Research, New York City, isolates gramicidin from soil bacterium *Bacillus brevis*. This becomes the first polypeptide antibiotic and the first antibiotic to be produced commercially, though it proves too toxic for any but external use.

1940. Stimulated by Dubos' success, Selman A. Waksman, microbiologist at Rutgers University, sifts through soil molds and isolates actinomycin. In 1942 he reports streptothricin and in 1943 streptomycin. Waksman coins the word antibiotic. Streptomycin, the first of the aminoglycosides, proves effective against gram-negative and anaerobic bacteria, whereas penicillins known to date act against only gram-positive aerobes. Waksman wins a Nobel Prize for streptomycin in 1952.

1943. Chemists William B. Stillman, A. B. Scott, and J. M. Clampit at Norwich Pharmacal Co. report nitrofurazone as the first of the nitrofuran antibacterial drugs.

1947. John Ehrlich isolates chloramphenicol from *Streptomyces venezuelae*, which is both a rare example of a nitrochloro compound in nature and a broad-spectrum antibiotic.

1948. Botanist Benjamin M. Duggar retires from the University of Wisconsin, goes to work for Lederle Laboratories, and isolates aureomycin from *S. aureofaciens*, thereby discovering the first of the tetracyclines.

1952. James McGuire of Eli Lilly isolates erythromycin from *S. erythreus*.

1957. P. Sensi of Lepetit isolates rifamycins, the first of the ansamacrolides, from *Nocardia mediterranei* in a project code-named "Rififi" after the then-popular movie and modifies one of them chemically to rifampin.

1962. Chemists George Y. Lesher and Monte D. Gruett of Sterling Drug Co. report nalidixic acid as the first of the quinolone antibacterial drugs. Donald J. Mason, Alma Dietz, and Clarence DeBoer of Upjohn isolate lincomycin, the first of the lincosaminides, from *S. lincolnensis*.

1975. Workers at Merck isolate thienamycin from *S. cattleya*, the first of the carbapenems, and develop it into Primaxin, the widest spectrum antibacterial known to date.

1980. Scientists at Squibb isolate the first of the monobactams after a massive screening of soil molds.

1986. The U.S. antibacterial drug market tops $2.5 billion, heading toward $3 billion in 1990. Medicinal chemists pursue such compounds as monobactams, carbapenems, and quinolones in vigorous efforts to outflank bacterial resistance and meet pressures to cut treatment costs.

Spiro: either extend spectrum of coverage or enhance usefulness

the infecting microbe. Previously, doctors have sometimes prescribed a combination of drugs that includes penicillin or cephalosporin and an aminoglycoside. The purpose of the aminoglycoside is to ensure that such stubborn, gram-negative bacteria as *Pseudomonas aeruginosa* are eradicated.

The nursing and pharmacy costs of using a single antibacterial are lower than those of prescribing a combination of drugs. Omitting an aminoglycoside also avoids the cost of laboratory testing for signs of kidney and hearing damage that aminoglycosides can cause. Merck prices Primaxin higher than penicillins, cephalosporins, and aminoglycosides. But the company has estimated that the total cost of a course of Primaxin is less than that of combinations.

Pfizer's cefoperazone has broad activity against gram-positive and gram-negative bacteria and can be given as a single agent twice daily, which cuts costs in comparison with other drugs or combinations given more frequently. The company also has guaranteed that if a hospital uses cefoperazone, and if the patient's hospital stay exceeds the length that medicare reimburses under DRGs, then Pfizer will replace the "extra" cefoperazone free.

The problems and opportunities of the changing U.S. antibacterial

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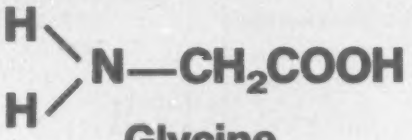

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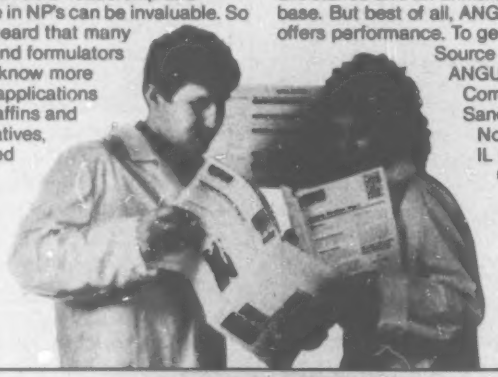

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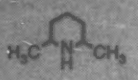
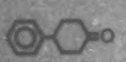


2,6-Dimethylpiperidine, cis



4-Phenylcyclohexanone

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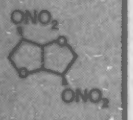
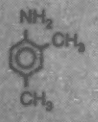
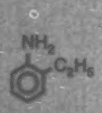


2,4-Xylidine and all other isomers



2-Ethylaniline and 4-Ethylaniline



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Antibiotic plant designs emphasize sterility

To design and build antibiotic fermentation plants, drug companies often turn to such engineering firms as Catalytic, Crawford & Russell, Davy McKee, and Foster Wheeler. Largest in the field is Foster Wheeler, whose antibiotics projects under way worldwide total $500 million.

To Tele Gnudi, Foster Wheeler's technical director for pharmaceuticals and fine chemicals, the dominant theme of plant design is maintenance of sterile conditions in the face of demands for quick turnarounds of main fermentors between batches. Invading microbes can easily overwhelm antibiotic-producing molds in fermentors, causing loss of a batch and the several weeks' time to produce it.

A 10,000- to 90,000-gal batch begins in the laboratory, where workers break open a frozen vial of antibiotic-producing organism and culture it in flasks increasing in size from 250 mL to 5 L over a period of 12 days to provide an inoculum for the industrial section. They also propagate and maintain this high-productivity strain and freeze it in new vials at liquid-nitrogen temperatures.

In the industrial section of the plant, operators grow the organism for two to three days in two 100-gal seed fermentors, then for two to three days in two 1000-gal germinators, before transferring it to, for example, a 10,000-gal main fermentor. Seed fermentors and germinators are run in pairs as a backup in case something happens to one inoculum.

Assays usually show that antibiotic production has peaked after 30 days at 25 to 28 °C in the main fermentor. The mixture is cooled to 10 °C, treated with formaldehyde, and pumped over 10 to 20 minutes to a harvest tank. Other workers take a week to extract and purify the antibiotic. Meanwhile, operators of the main fermentor take 10 hours to clean it, sterilize it with 145 °C steam, and start a new batch. Molds from production batches are now unproductive mutants, so new batches must start with inoculum from the lab.

Gnudi sizes the lab and the rest of the plant around staggered scheduling of the 30-day run times of the number of main fermentors needed to achieve desired capacity. In this way, he minimizes capital investment in support equipment and maximizes use of the main fermentors. The lab must have a gowning room for workers to dress, a laundry room for gowns, a clean room to open frozen vials, and an incubator room. Avoiding architects' "standard" designs, Gnudi designs the lab and specifies furnishings after analyzing what work must be done there and what the equipment needs are.

In the industrial section, Gnudi's chief concerns in designing main fermentors are efficient operation and fast, thorough cleaning. He often specifies stainless steel, though carbon steel, copper, or glass fiber-reinforced polyester may be used. He pays careful attention to welds and polishing the interior to avoid crevices, minimizes such interior fittings as baffles and coils, leaves space to clean around and behind fittings, and installs the compressed air pipe at the bottom rather than all the way down the inside from the top.

Gnudi points out that a vertical, 30-foot-high, 20,000-gal fermentor needs a building 50 feet high and a foundation sufficient to support its weight on a 100-sq-ft area. He has sometimes reduced costs by placing fermentors horizontally in a 20-foot-high building with only their heads inside and the rest outdoors. Supporting horizontal fermentors in two places reduces the load that foundations bear. He then uses two agitators rather than one, driven by a single diesel engine. For vertical fermentors, he supports agitator motors from the floor rather than on the heads.

Another concern is sterile nutrients. These are mixtures of sugars, molasses, starch, soybean meal, cracked corn, and/or (for penicillin) corn steep liquor in water with calcium carbonate and salts. Gnudi's plants mix these in a storage tank and pass the mixture through a plate heat exchanger for heating to 121 °C with a residence time of two to four minutes. This continuously sterilized medium goes from the heat exchanger to a second storage tank from which it is fed by a metering pump to fermentors.

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Yet another concern is sterile air. Gnudi favors the high flow rates of centrifugal positive displacement compressors to generate this, though the 120-decibel noise level of these compressors force him to place them in separate buildings. Compressed air is chilled to condense out moisture, which might foul membranes or filters. Gnudi's clients may elect to pass moderately cooled air through a polytetrafluoroethylene membrane or thoroughly chilled and reheated air through a 0.2-μm glass filter.

They may also elect to pass anhydrous ammonia into fermentors with the air as a nitrogen source, though this requires a delicate balance of conditions to avoid outgassing of ammonia again by the air. Alternatively, ammonium phosphate salts may be added, thus controlling pH and providing nitrogen simultaneously.

For plants that produce many antibiotics, Gnudi takes care to avoid cross-contamination of products. He uses special care to isolate penicillin or cephalosporin from other production, because of the dangers of penicillin allergies. These units may be protected by scrubbers and have their own laundries.

From the main fermentor and harvest tank, the fermentation mixture goes to a rotary vacuum filter to remove the mycelium, which is the mass of filaments that molds grow. Most antibiotics are dissolved in the filtered broth, though griseofulvin is one that remains with the mycelium and must be extracted with solvents.

Depending on the antibiotic, the drug may be isolated from filtered broth by countercurrent extraction with acetone, methylisobutyl ketone, or butanol; reverse osmosis; adsorption, ion exchange, or chromatography; precipitation; or simple evaporation. The powder remaining after the final evaporation is nonsterile, technical-grade antibiotic.

This may be sold as animal feed additive or processed to sterile antibiotic for making up dosage forms. Gnudi's clients may use a sterile section of the same plant for this purpose, send the antibiotic to another location that has one, or sell it to another drug firm.

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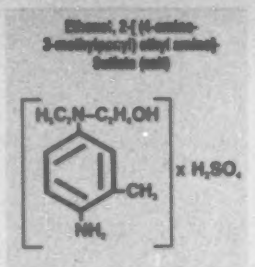

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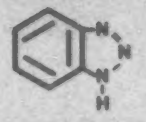

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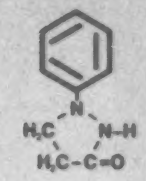

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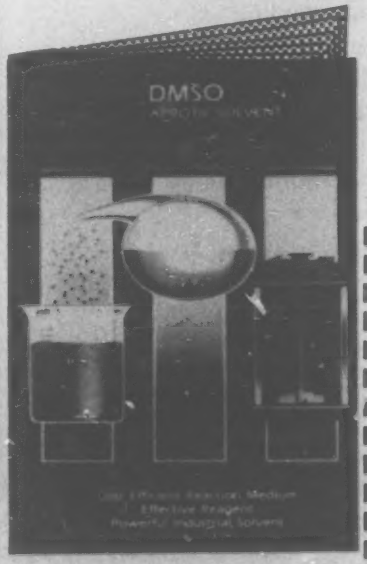

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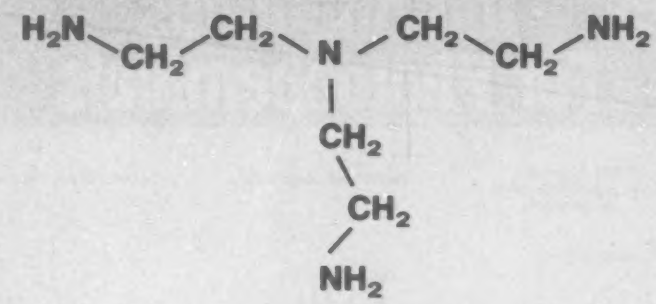

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Antibacterial drug sales to grow 5% annually

$ Millions	1985	1990
INJECTABLE ANTIBACTERIALS	$1388	$1518
Cephalosporins	765	888
First generation	207	154
Second generation	342	350
Third generation	216	384
Gram-positive drugs	180	160
Aminoglycosides	121	85
Extended-spectrum penicillins	193	185
Monobactams	0	60
Penems and carbapenems	0	95
Other	129	45
ORAL ANTIBACTERIALS	1109	1509
Cephalosporins	446	645
Tetracyclines	136	123
Erythromycins	144	162
Amoxicillin	59	75
Quinolones	0	155
Other	240	174
TOTAL	$2497	$3027

Source: Sanford C. Bernstein & Co.

market have attracted several drug companies new to antibacterials. By far the leader to date has been Eli Lilly & Co. Crossen of Bernstein & Co. estimates that Lilly's antibacterial sales in 1985 were $719 million, or almost 30% of the market.

Crossen sees great promise for Lilly's new injectable cephalosporin, ceftazidime, which may become the drug of choice for *P. aeruginosa*. He notes, however, that Glaxo and Smith Kline & French Laboratories will compete in the ceftazidime market. Lilly's sales of its older oral cephalosporin, cefaclor, also will continue well through 1990 before meeting competition from other antibacterials, Crossen says.

But such progress cannot offset market losses owing to newer antibacterials from other firms and the expiration of patents on some of Lilly's older compounds. Crossen estimates that in 1990 the company's antibacterial sales will total $596 million, still in the lead, but not quite 20% of the U.S. market.

Among companies making new efforts in antibacterials in the U.S. are Ciba-Geigy, Hoffmann-La Roche, Merrell Dow Pharmaceuticals, Ortho Pharmaceutical Corp. (subsidiary of Johnson & Johnson), Parke-Davis (division of Warner-Lambert), and Stuart Pharmaceuticals (subsid-

iary of ICI Americas). Crossen estimates that combined antibacterial sales of these new-entry firms could total about $290 million in 1990, which will be almost 10% of the U.S. market, compared with zero today.

In addition, Schering Corp., whose sales were limited to $9 million worth of gentamycin in 1985, may see sales of $30 million in 1990, owing to approval of an injectable β-lactam called Sch-29,482. And the quinolone amifloxicin may contribute $5 million to sales of Sterling Drug Co. in 1990. Over the past 25 years, Sterling has had minor sales of nalidixic acid, the first quinolone to be discovered..

Timothy P. Spiro, director of clinical research on metabolic and infectious diseases at Hoechst-Roussel Pharmaceuticals, Somerville, N.J., says that if a new drug is to be successful, it must either extend the spectrum of coverage or represent a scientific advance that enhances usefulness.

Hoechst-Roussel has already had considerable success with its cefotaxime injectable cephalosporin. Many doctors use it as the first line of attack for meningitis or bacteremia, for which antibiotics must be started immediately, before the organism or its antibacterial susceptibility is known.

Spiro's example of a broader-spectrum drug is cefpirome, an injectable cephalosporin that the company is putting through the U.S. approval process. Cefpirome's broader spectrum includes increased activity against difficult organisms like *P. aeruginosa*, enterococci, and methicillin-resistant staphylococci. Methicillin resistance is one hallmark of bacteria that are resistant to the newer cephalosporins also and causes concern in hospitals where such strains have begun to proliferate.

Cefpirome also resists antibiotic-inactivating β-lactamases and has a longer half-life than cefotaxime, leading Spiro to suggest the possibility of giving it only twice daily. Such a possibility would add cost savings to cefpirome's other advantages.

Roxithromycin is Spiro's example of a drug that enhances usefulness. Hoechst-Roussel is also working toward U.S. approval of this 2-methoxyethoxymethoxylimino derivative of erythromycin. The oral drug erythromycin itself has a large market in the U.S. because it is favored by pediatricians and general practitioners in office practice. It is very safe, especially among children, and attacks fungal as well as gram-positive bacterial infections.

But erythromycin is poorly absorbed in the body and can cause unpleasant gastrointestinal side effects. Spiro says that roxithromycin is much better absorbed, has a longer half-life, and has the same spectrum as erythromycin.

George B. Mackaness, president of Squibb Institute of Medical Research, has a somewhat different philosophy regarding drugs. His

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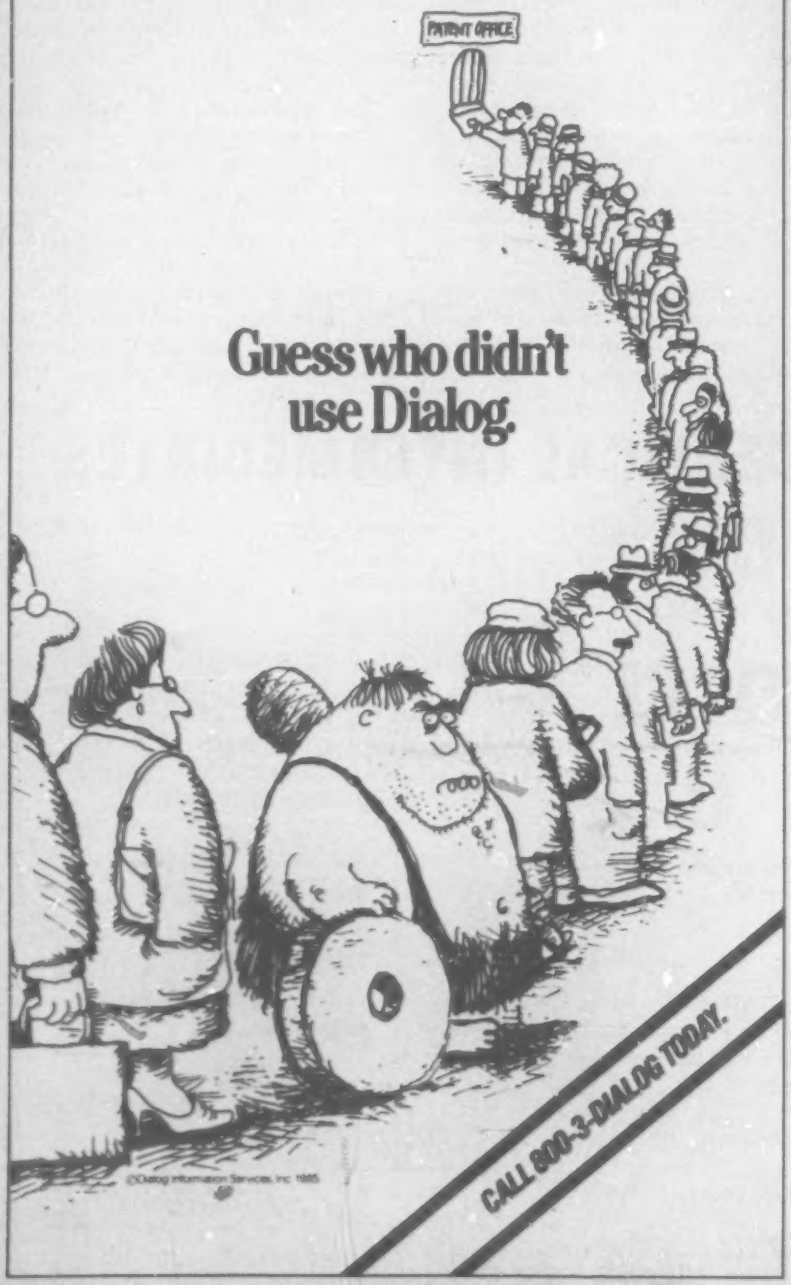

CIRCLE 18 ON READER SERVICE CARD

Squibb photo

Photomicrograph of antibiotic aztreonam, tradenamed Azactam

company has dissociated itself from the broad-spectrum approach to therapy and is developing aztreonam, an injectable specific against *P. aeruginosa* and other aerobic (oxygen-requiring) gram-negative bacteria. The compound is inactive against gram-positive organisms or anaerobes (those inhibited by oxygen). Further in the future is approval of tigemonam, an oral monobactam with a narrow spectrum similar to that of aztreonam. Both aztreonam and tigemonam resist β-lactamases.

"Time will establish, I think, that a more careful approach is required," says Mackaness of antibiotic therapy. He suggests that doctors may use combinations of antibiotics as a first attack on emergency infections, including aztreonam to cover gram-negative bacteria. Thus, the expense of monitoring patients for adverse reactions to aminoglycosides would be avoided. As tests come back from the laboratory, doctors can withdraw those agents from the combination that are not effective.

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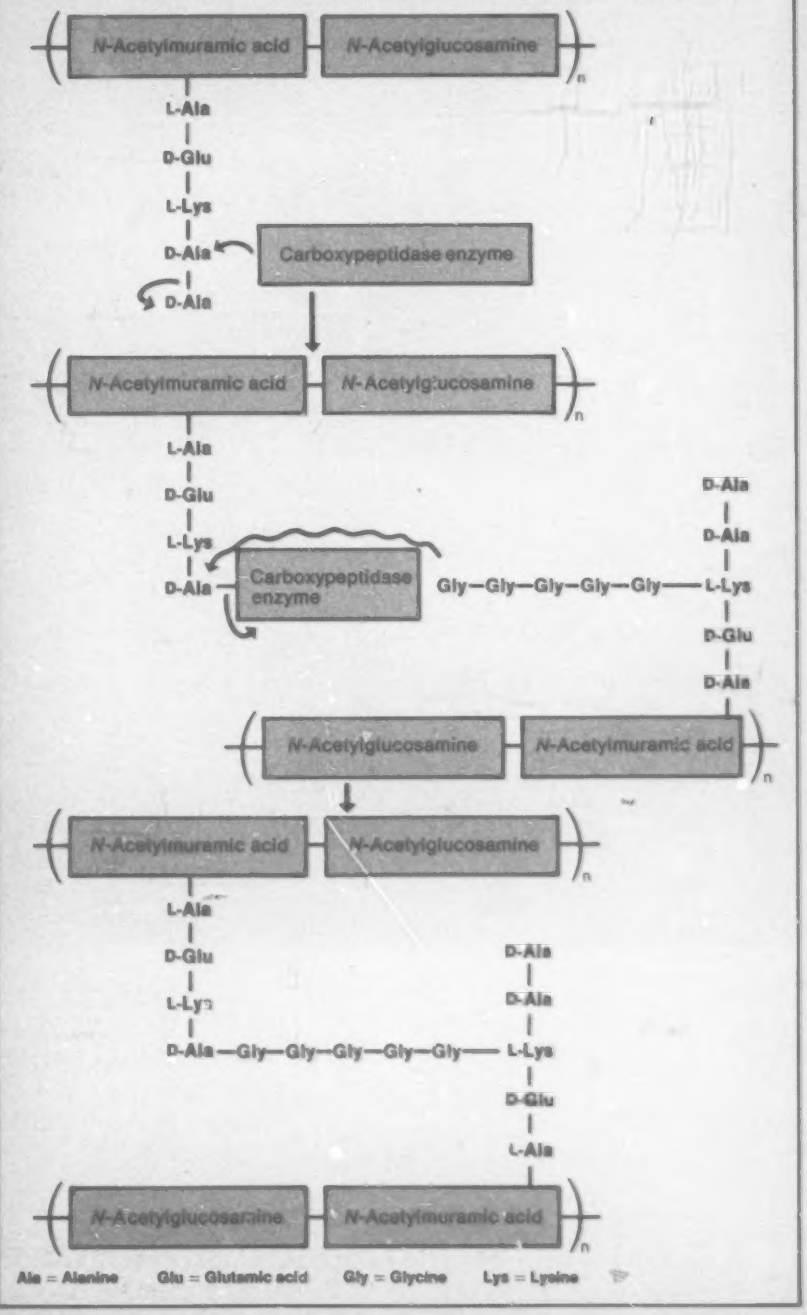
Mackaness' concern is that use of broad-spectrum antibiotics leads to development of bacteria in hospitals that are resistant to β-lactams generally. "Broad-spectrum antibiotics deal a broad blow to all organisms," he says. "They put all organisms under pressure to develop resistance." Patients who get broad-spectrum antibiotics in doctors' offices may later be admitted to hospitals, where they will spread resistant strains. Moreover, eliminating gram-positive bacteria may cause an overgrowth of resistant aerobic gram-negative bacteria in hospital air.

Even further in Squibb's future is a second-generation monobactam known now as SQ-83,360. The min-

Bacteria build cell walls by crosslinking peptidoglycan



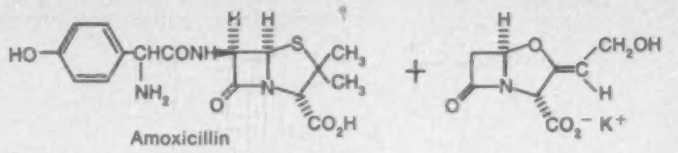
imal inhibitory concentration of this compound against *P. aeruginosa* is 0.5 μg per mL, compared with 12.5 μg per mL for aztreonam or cephalosporins. Mackaness suggests that a dihydroxypicolinoyl group on this molecule may complex iron, and thus may be absorbed by *P. aeruginosa* cells by the same route the organism uses to transport iron.

As medicinal chemists at Squibb and other firms seek to broaden (or narrow) the spectrum of antibacterials and to overcome evolving resistant bacteria, screening compounds from natural sources goes hand in hand with chemical modification of natural products. For example, Squibb scientists discovered monobactams by fermenting molds from soil samples. No living organism ever made aztreonam, the first monobactam to be commercialized. And when it goes on the market here, Squibb will produce it with totally synthetic methods.

As far as screening for new antibiotics is concerned, there is a rough division between screening for β-lactams and for all others. One reason for this is that β-lactams have an almost unparalleled record of safety in humans. Aminoglycosides must be monitored for kidney and otic nerve toxicity. Tetracyclines stain children's teeth. Only erythromycins avoid such problems though they are effective mostly against gram-positive bacteria.

Some patients do develop aller-

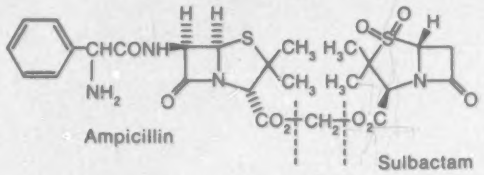
Some firms mix β-lactamase inhibitors with antibiotics . . .



Amoxicillin + Potassium clavulanate

Augmentin (Beecham)

. . . but others combine inhibitors covalently



Ampicillin — Sulbactam

Sultamicillin (Pfizer)

Note: Augmentin is the tradename for the mixture of amoxicillin and potassium clavulanate. Sultamicillin is the generic name for covalently bonded ampicillin and sulbactam.

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gic hypersensitivity to β-lactams. Allergic reactions can be fatal. But even here, medicinal chemists have found β-lactams that avoid reactions in sensitive patients. And the effectiveness of penicillin G against bacterial meningitis is so great that some doctors will still give it to patients who have never had an immediate reaction to it, and then be prepared to treat a reaction.

A second reason for seeking new β-lactams specifically is that their chemistry, the molecular biology of bacterial resistance to them, and means to get around resistance have been more thoroughly worked out than for any other class. A fruitful cycle of research has evolved in which medicinal chemists' and molecular biologists' efforts have been rewarded with revealing and profitable results, leading to redoubled efforts.

One example of the desirability of β-lactams as commercial products is the saga of the development of Primaxin at Merck. Scientists there first reported isolating thienamycin from *Streptomyces cattleya* in 1976. Though thienamycin had the potential of having the broadest spectrum ever seen in an antibiotic, it was unstable.

Unwilling to give up on the compound, Merck chemists modified the basic molecule until they hit upon the *N*-formimidoyl derivative of the aminoethylthio side chain, which was stable. Further testing of this compound, called imipenem, showed that it was hydrolyzed by a human kidney enzyme called dehydropeptidase-1. This meant that imipenem could never achieve high concentrations in urine, thus rendering it useless for urinary tract infections.

Merck chemists turned to searching for an inhibitor of dehydropeptidase-1 and found one in cilastatin. A 1:1 mixture of imipenem and cilastatin produced therapeutic concentrations of imipenem in human urine.

But a physical mixture of two agents was bound to raise questions at FDA. This is because for more than 20 years the agency had traditionally judged such products "ineffective as a fixed combination." That is, Merck would have to show clinical proof that a 1:1 ratio of

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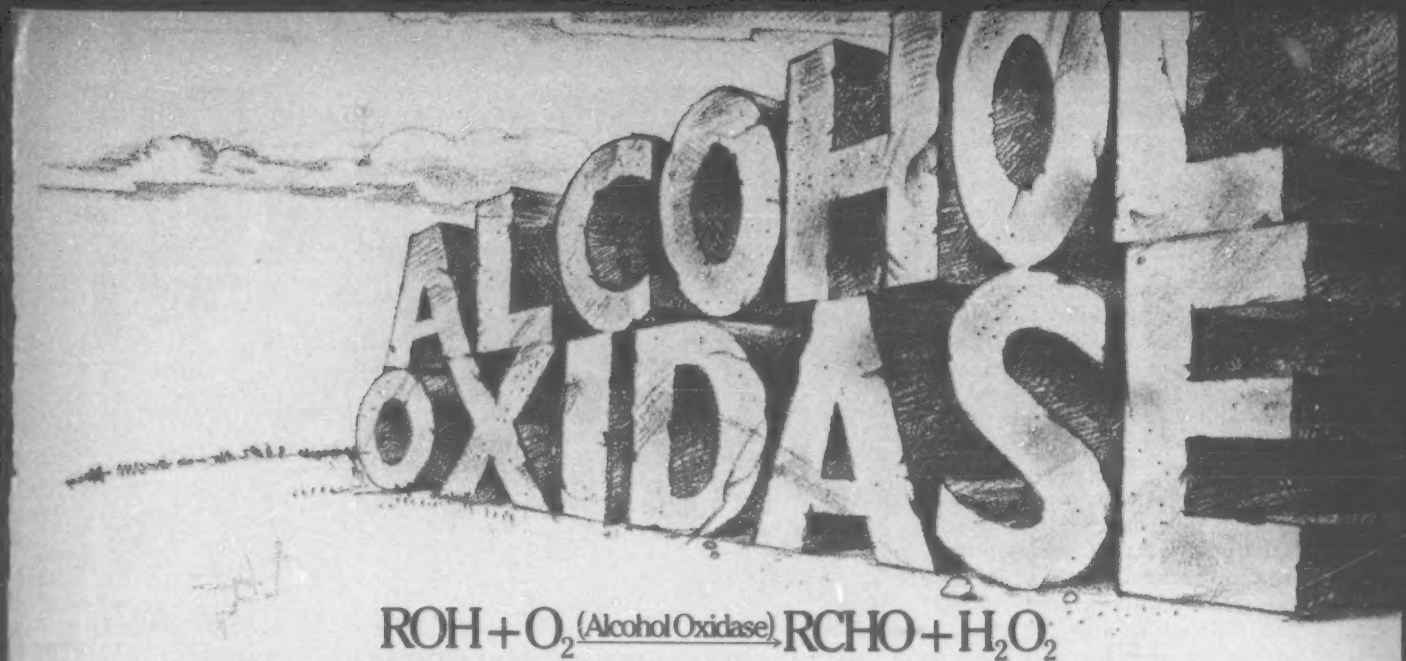

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imipenem to cilastatin was not arbitrary but uniquely necessary for effectiveness. Merck scientists developed this evidence, and FDA approved the combination drug, now tradenamed Primaxin, in 1985.

In their search for new β-lactams and other antibiotic types, medicinal chemists make use of increasingly sophisticated screening methods. The screening program that uncovered the monobactams for Squibb, for example, depended on whether or not fermentation broths would stimulate bacteria to produce β-lactamases.

Squibb scientists grew cultures of *Bacillus licheniformis* on agar medium in petri dishes. This bacterium has a gene for a β-lactamase in its chromosome, but the enzyme is normally produced at very low levels. When exposed to a β-lactam, however, *B. licheniformis* responds by producing large amounts of the destroying enzyme.

The Squibb workers impregnated paper disks with fermentation broths from soil samples and laid the disks over the agar. After two to three hours of incubation, nitrocefin solution was applied to the cultures. Appearance of a red color around a disk indicated that the fermentation broth applied to that disk contained a β-lactam.

If a β-lactam was present in the fermentation broth, the *B. licheniformis* would produce large amounts of β-lactamase around that disk. The β-lactamase would hydrolyze the β-lactam group of nitrocefin, yielding the equivalent of a β-amino-*p*-styrene, whose red color would be the telltale sign.

The Squibb test was sensitive to as little as 1 ng of β-lactam, compared with 15 ng needed in bacterial growth inhibition tests and 200 to 3000 ng for tests that depend on observing changes in bacterial shape. The Squibb program yielded new β-lactams at the rate of one per 1 million tests, but the monobactams the company will bring to market as a result will more than repay the effort.

One expert in development of sophisticated, new, antibiotic screening techniques is Louis J. Nisbet. Nisbet has recently founded Xenova, a company that will offer screening services for antibiotics and compounds with other pharmacological activity. Currently, Xenova's offices are in London, but Nisbet plans permanent offices and laboratories near Oxford, England.

One such β-lactam screening method that Nisbet has developed depends on inhibiting D,D-carboxypeptidase. This enzyme cleaves a terminal D-alanine group from a pentapeptide side chain of bacterial peptidoglycan. Peptidoglycan is the sugar-peptide substance that forms bacterial cell walls. Cleavage of D-alanine from its pentapeptide side chain is the first step in reactions that crosslink peptidoglycan to form finished cell wall substance. β-Lactam antibiotics interfere with the crosslinking process, leading eventually to bursting of the bacterium.

Nisbet synthesized a uridine diphosphate/*N*-acetylmuramyl derivative of the pentapeptide as a model compound for peptidoglycan. He next isolated a D,D-carboxypeptidase from a Streptomycete mold. He added purified D,D-carboxypeptidase to a sample of fermentation broth. If the broth contained a

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β-lactam, this would inhibit the D,D-carboxypeptidase. Then he added the pentapeptide derivative. If a β-lactam had inhibited the D,D-carboxypeptidase, the pentapeptide would not be degraded. If no β-lactam was present, then the pentapeptide would be hydrolyzed to a tetrapeptide. Nisbet analyzed for tetra- and pentapeptide with high-performance liquid chromatography.

Another screening method developed by Nisbet is for glycoprotein antibiotics of the vancomycin type. Vancomycin is important because doctors often rely on it as a second line of attack against the growing number of gram-positive bacteria like Staphylococci and Streptococci that are resistant to β-lactams. This antibiotic is also life-saving in cases of pseudomembranous colitis, a destructive irritation of the intestinal lining caused by a toxin of *Clostridium difficile*. This bacterium sometimes grows out of control after other intestinal bacteria have been killed by some antibiotics. Vancomycin destroys *C. difficile*.

Constant screening uncovers new antibiotics at Squibb

Vancomycin kills bacteria by binding tightly to the D-alanyl-D-alanine group at the end of the peptidoglycan pentapeptide side chain. This action prevents crosslinking of peptidoglycan to form bacterial cell wall substance. Nisbet's screen for vancomycinlike activity uses *N,N'*-diacetyl-L-lysyl-D-alanyl-D-alanine as a model of the end of the pentapeptide side chain.

He impregnates two paper disks with the fermentation broth to be tested. He then impregnates one of

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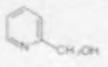
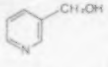
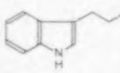
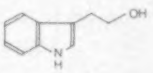
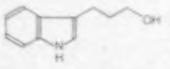
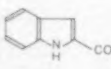
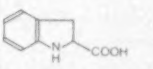
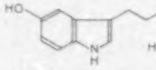
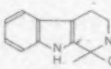
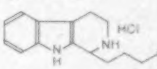
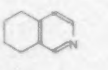
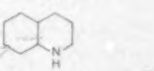
2-pyridine methanol 	3-pyridine methanol 	4-pyridine methanol
Indoline	Tryptamine 	Tryptophol 
Homotryptophol 	Indole-2-carboxylic acid 	Indoline-2-carboxylic acid 
Serotonin hydrochloride 	1-Methy-1-metoxycarbonyl-tetrahydro-β-carboline hydrochloride 	1-Hydroxypropyl-tetrahydro-β-carboline hydrochloride 
1,2,3,4-Tetrahydroquinoline	5,6,7,8-Tetrahydroisoquinoline 	Decahydroquinoline 

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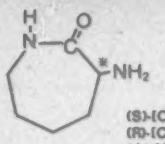
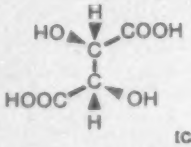


(S)-[CAS No. 21568-87-6]
(R)-[CAS No. 28957-33-7]
(±)-[CAS No. 17929-90-7]

D(-)-Tartaric Acid

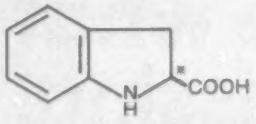


[CAS No. 147-71-7]

APPLICATIONS:

- Optical Resolution Reagent
- Asymmetric Synthesis Catalyst
- Chiral Intermediates

Indoline-2-Carboxylic Acid



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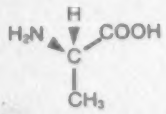
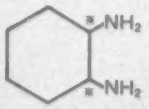
(R)-[CAS No. 98167-06-7]
(±)-[CAS No. 16851-56-2]

D(-)-Alanine



[CAS No. 338-69-2]

Trans-1, 2-Diaminocyclohexane



(R,R)-[CAS No. 20439-47-8]
(S,S)-[CAS No. 21436-03-3]

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these disks also with the tripeptide model compound. He lays the disks over a "lawn" of bacteria on agar medium in a petri dish.

If the disk impregnated only with broth shows a zone of inhibition (a circle around the disk free of bacteria), Nisbet knows that the broth contains an antibiotic. If at the same time the disk impregnated with both broth and tripeptide shows a small or no zone of inhibition, he concludes that the antibiotic has vancomycinlike activity. This is because the tripeptide binds the antibiotic in the broth, leaving little or none to inhibit bacterial growth.

Nisbet notes that screening soil molds for vancomycin-type antibiotics turns up one new compound for every 320 tests. This compares with one compound in 10,000 to 100,000 tests using other methods. Nisbet concludes that such natural sources as molds are even richer in new antibiotics than previously suspected. Some of these compounds have value in an unmodified state. The molecular structures of others can be modified by medicinal chemists to develop even greater potency.

In addition to screening natural sources for β-lactam, vancomycin, or other known activity, microbiologists have turned recently to so-called nonclassical screening techniques. Traditionally, workers have discovered antibacterials by a shotgun approach, according to whether they produced zones of inhibition around disks. Then they study what particular antibacterials do to kill bacteria.

These studies resulted in identification of six mechanisms by which antibacterials disrupt bacterial metabolism. These six mechanisms were inhibition of biosynthesis of nucleic acids, biosynthesis of peptidoglycan, biosynthesis of lipids, functions of ribosomes (which mediate biosynthesis of proteins), functions of membranes (such as transport of certain substances in and out of bacterial cells), and metabolism of folic acid. Workers then developed screening methods to detect compounds active by one of these six classical mechanisms.

Knowledge of the six classical mechanisms is valuable because they affect processes unique to bac-

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teria. Thus, compounds that disrupt these processes are likely to be nontoxic to human cells. But other processes are also known to be unique to bacteria, and it is disruption of these to which medicinal chemists now turn to screen for new antibacterials.

For example, gram-negative bacteria surround their peptidoglycan cell walls with a membrane that consists mostly of murein lipoprotein. The antibiotic globomycin prevents conversion of an intermediate prolipoprotein to lipoprotein, causing the prolipoprotein to accumulate in the cytoplasmic membrane lying just under the cell wall, and leading eventually to bursting of the cell. Another component of the outer membrane of gram-negative bacteria is lipopolysaccharide. Chemists at Sandoz have developed a synthetic thienodiazaborine that apparently prevents conversion of D-arabinose 5-phosphate to a substance called KDO, which is a component of lipopolysaccharide.

Nonclassical screening techniques also may prove valuable for discovering compounds that are not antibacterials themselves, but potentiate the actions of antibacterials. One such class of compounds are the β-lactamase inhibitors, which include clavulanic acid, olivanic acid, and sulbactam.

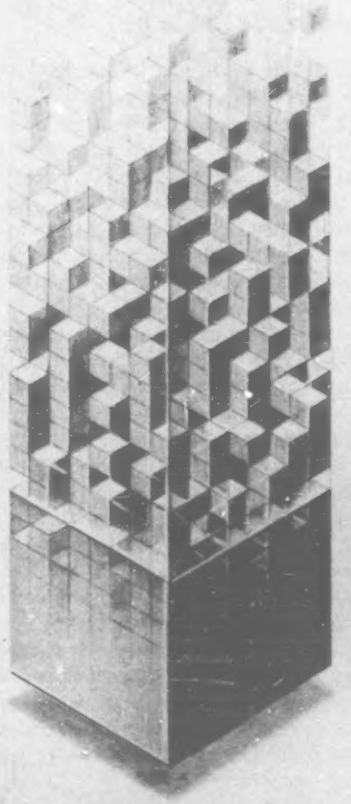
Beecham Laboratories has developed mixtures of the semisynthetic penicillins amoxicillin and ticarcillin with clavulanic acid. This development has preserved the usefulness of these workhorse penicillins against infections by bacteria that produce β-lactamases.

Moreover, β-lactamases made in large amounts by resistant bacteria may be secreted from them and form a protective umbrella for pathogens that do not produce β-lactamases themselves. Thus, combinations of β-lactams and β-lactamase inhibitors break through this protective umbrella as well as attack β-lactamase producers themselves.

Pfizer has developed mixtures of sulbactam with its new cephalosporin cefoperazone and the semisynthetic penicillin ampicillin. The company has also synthesized sultamicillin, an oral drug that is a mixed

Squibb photo

Culture of bacteria from soil examined for ability to produce antibiotics



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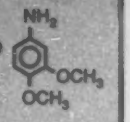
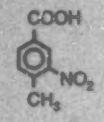
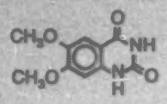


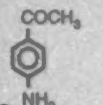
3-Nitro-p-toluic acid
and other isomers



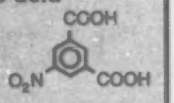
6,7-Dimethoxy-
quinazoline-2,4-dione



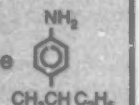
4-Aminoacetophenone



5-Nitroisophthalic acid
and derivatives



4-*sec.* Butylaniline
and 2-*sec.* Butylaniline



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acetal of ampicillin and sulbactam with formaldehyde. The two ampicillin products may be approved in the U.S. in 1987.

The covalent linking of ampicillin and sulbactam makes sultamicillin a prodrug, which is transported to the infection site and hydrolyzed to the antibiotic and β-lactamase inhibitor. It may also allay the concerns of FDA about fixed combinations of drugs.

In approving Beecham's oral amoxicillin and injectable ticarcillin products, regulators at the agency may have reasoned that the products were important advances and that the two components have different, complementary functions. Some doctors caution, however, that in giving a 500-mg dose of the amoxicillin product, one 500-mg tablet should be prescribed rather than two 250-mg tablets. This is because both forms contain 125 mg of clavulanic acid, and two 250-mg tablets may deliver too much clavulanic acid.

In addition to screening natural sources for antibiotics, medicinal chemists sometimes discover classes of wholly synthetic antibacterial drugs. Examples are the sulfa drugs discovered in 1932, the nitrofurans discovered in 1943, and the quinolones discovered in 1962.

Sulfa drugs have a few important roles in modern antibacterial therapy, though they have been largely eclipsed by antibiotics. Sulfisoxazole is among drugs recommended for urinary infections. A combination of sulfamethoxazole and trimethoprim is important for certain urinary, middle ear, and bronchial infections. Sulfa drugs are thought to be mimics of *p*-aminobenzoic acid, an intermediate in bacterial folic acid synthesis. Trimethoprim is a wholly synthetic benzylpyrimidine that antagonizes folic acid.

Quinolones have received renewed attention since about 1980, owing to invention of 6-fluoro analogs that have lower incidences of side effects, reduced development of bacterial resistance, and greater bioavailability. When these new an-

Staining helps doctors plan antibiotic therapy

When doctors suspect a bacterial infection, they order cultures of sputum, blood, or spinal fluid to identify the bacteria and measure their susceptibilities to antibiotics. Testing often includes swabbing fluid onto agar, placing 12 paper disks impregnated with different antibiotics on the medium, and waiting 18 hours to see which disks have large areas clear of bacteria around them.

But for patients suspected of having such life-threatening infections as meningitis (infection of brain lining) or bacteremia (blood poisoning), antibiotics must be started at once. Cancer and transplant patients, as well as the elderly, whose immune systems are compromised, must also be treated aggressively. In such cases, doctors gain a head start both from immediate microscopic examination to determine bacterial shape and from gram staining.

For gram staining, a technician smears fluid from the patient onto a slide and dries it with quick passes over a flame. Then a stain such as gentian violet is flowed over the dried film. Next this color is fixed by flooding the film with alkaline iodine-potassium iodide solution. This is followed by a decolorizing wash with ethanol and application of a red second stain such as safranin. Bacteria that retain the initial violet stain are classed as gram-positive, whereas those that take the red counterstain are classed as gram-negative.

Gram-positive bacteria are surrounded by their peptidoglycan cell walls, and gram-negative organisms have a lipid layer over the peptidoglycan. Lipid outer layers stain differently from peptidoglycan and resist penetration by some antibiotics. Structures called porins in lipid layers render gram-negative bacteria susceptible to other antibiotics, however.

One variation of the gram method uses a red stain like carbol fuchsin as the first stain, ethanolic hydrochloric acid instead of ethanol as decolorizer, and methylene blue as the second stain. Such acid-fast bacteria as *Mycobacterium tuberculosis* appear red; others appear blue.

alogs come to market in the U.S. beginning in 1987, they are expected to play an important role because they are oral drugs, which can be dispensed more cheaply than injectables. Their production may also be cheaper because they are made by organic synthesis rather than by fermentation and semisynthetic modification. Price competition among the half-dozen expected to be approved in the U.S. by 1990 may accelerate the passage of lower costs to patients.

Quinolones act by inhibiting DNA gyrase. This enzyme mediates the uncoiling of DNA during replication of circular bacterial chromosomes and the separation of the two circular chromosomes afterwards. Inhibiting this process is lethal in bacteria.

The first quinolones marketed in the U.S. carried a high incidence of gastrointestinal disturbances and of side effects in the central nervous system such as disturbed vision, dizziness, and seizures. The newer compounds show such side effects in less than 5% of patients. Concern continues about mediation of cartilage erosion by even the newer quinolones in very young laboratory animals. Because of this concern, they will be contraindicated for children.

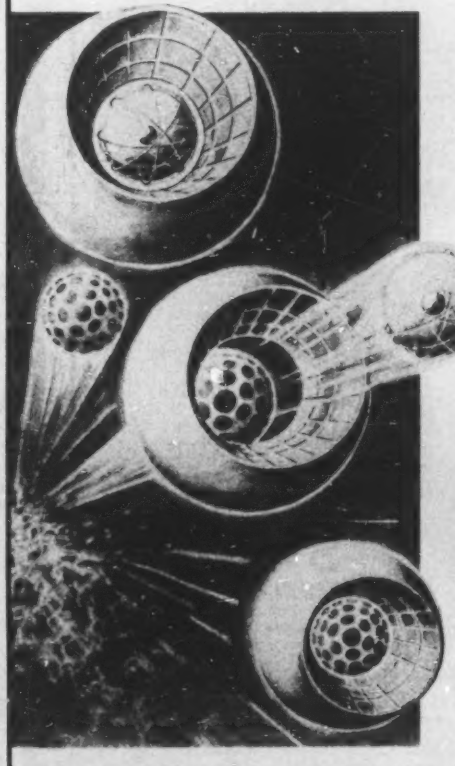
A second disadvantage of the early quinolones was that they were poorly absorbed in the bloodstream. They did achieve high concentrations in urine, however, leading to their use in urinary infections. Absorption of the newer compounds is much better.

Third, patient-infecting bacteria tended to develop resistance to early quinolones quickly. Some workers have suggested that bacteria were able to modify their cell walls or membranes in such a way as to shut out the quinolone molecules. The 6-fluoro derivatives show much slower development of resistance.

Although the virtue of the quinolones is that they are broad-spectrum oral drugs, some doctors would like to see injectables developed. This is because patients do not eat or drink for a few days after surgery, and anesthetics render their digestive systems inactive. Others may have gastrointestinal disease and be unable to tolerate oral drugs.

Pefloxacin is a quinolone that has had some success as an injectable as well as an oral drug in France. No company is thought to be developing the drug for the U.S. market, however.

Security analyst Vietor at Merrill Lynch estimates that Merck will be first in the U.S. market with norfloxacin among the new generation quinolones, followed by the enoxacin of Parke-Davis. Miles Laboratories may or may not get approval for ciprofloxacin before Ortho does for ofloxacin. Both ciprofloxacin and ofloxacin have very broad spectra and could become important antibacterials in the U.S., even if the two other compounds are introduced first. □



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